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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,902	11/17/2000	John James Donnelly	1627.003	5612

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/715,902	DONNELLY ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 6/21/04.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-16,18-23,29-31,33-44,46,50,52 and 53 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-16,18-23,29-31,33-44,46,50,52 and 53 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and arguments received on 6/21/04 have been entered. Claims 1-16, 18-23, 29-31, 33-44, 46, 50, and 52-53 are currently pending and under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action, can be found in previous office actions.

Claim Rejections - 35 USC § 103

The rejection of pending claims 1-16, 18-23, 29-31, 33-44, 46, 50, and 52-53 under 35 U.S.C. 103(a) as being unpatentable over WO 97/24447, 7/10/97, hereafter referred to as Song et al., in view of US Patent No. 5,783,567 (7/21/98), hereafter referred to as Hedley et al., and further in view of Fattal et al. (1998) J. Controlled Rel., Vol. 53, 137-143, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claims for reasons of record as discussed in detail below.

The applicant reiterates their argument made in previous responses that the prior art cited by the office does not provide sufficient motivation or a reasonable expectation of success for making /using applicant's claimed invention, citing MPEP 2143 and *In re Mills* . As stated in previous office actions, it is noted that the test for combining references is not what the

individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). Furthermore, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). In the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. Most importantly, obviousness does **not** require absolute predictability of success; for obviousness under 35 U.S.C. 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

In response to applicant's arguments concerning each reference individually, it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant's arguments regarding the teachings of each reference are addressed below in the context of the combined teachings of Song et al., Hedley et al., and Fattal et al..

The applicant again acknowledges that Song et al. teaches several gene delivery vehicles for gene livery to dendritic cells, but reiterates their arguments that Song et al. does not teach a transfection agent comprising a polynucleotide and a microparticle as claimed, and that Song et al. demonstrates a preference for recombinant retroviral techniques over non-viral techniques.

The applicant further argues that neither Hedley et al. nor Fattal et al. overcome this deficiency in Song. As such, the applicant concludes that Song et al. in combination with the other cited references would only provide motivation for using recombinant retroviruses for *in vivo* transfection of dendritic cells. In response, and as discussed in detail in the previous office actions, Song et al. teaches methods of transfecting dendritic cells *ex vivo* or *in vitro* with a gene delivery vehicle comprising DNA encoding an antigen such as a tumor antigen or HIV antigen, and use of said transfected dendritic cells to induce an immune response against the expressed antigen in vivo (Song et al., pages 2, 3, and 18-20). Regarding gene delivery vehicles taught by Song et al., Song teaches that for *ex vivo/in vitro* transfection of dendritic cells, both non-viral and viral gene delivery vehicles can be used, including the use of expression vectors complexed with polycations or lipids or encapsulated in liposomes (Song et al., page 1, and pages 14-19). Thus, Song et al. teaches that numerous gene delivery vehicles can be successfully utilized to transfect dendritic cells including the use of plasmid/liposomes, and plasmid combined with cationic condensing agents. The fact that Song et al. exemplified retroviral transduction of dendritic cells does not invalidate the clear teachings in this reference that many techniques, including non-viral techniques, can be used to transfect dendritic cells *in vitro*. According to the applicants, the fact that Song et al. exemplified retroviruses teaches away from using non-viral vectors. However, this is not a fair reading of Song et al. Song et al. clearly teaches the use of other delivery vectors, specifically non-viral vectors. Again, a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). In response to applicant's citation of *In re Wesslau* and *Bausch & Lomb, Inc. v. Barnes-Hind/Hydorcurve, Inc.*, this body of case law is not on point. In the instant case, Song

et al. clearly teaches transfecting dendritic cells with non-viral vectors. Instead, the office points to *In re Susi* and *In re Gurley*, which state respectively: that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971); and, "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). Thus, the office does not find that Song et al. teaches away from using non-viral vectors simply because they exemplified the use of the retroviral vector rather than the use of the disclosed non-viral vectors. Furthermore, the applicant is reminded that the claims as written, which the exception of claim 16, do not place any limitation on the nature of the polynucleotide. Only claim 16 is limited to a plasmid. Claims 1-15, 18-23, 29-31, 33-44, 46, 50, and 52-53 read on the use of any polynucleotide.

In regards to applicant's argument that Song et al. does not teach the use of microparticles, Hedley et al. and Fattal et al. have been cited to supplement the teachings of Song et al. Regarding the teachings of Hedley et al., the applicant argues that Hedley primarily teaches the use of microparticles to transfect macrophages and that the only motivation for transfecting dendritic cells lies in *in vivo* rather than *in vitro/ex vivo* techniques. In response, Hedley et al. has been cited for the use of microspheres comprising biodegradable polymers and DNA plasmids to introduce and express antigens encoded by the plasmids in antigen presenting cells such as macrophages and dendritic cells both *in vitro* and *in vivo* for the purpose of stimulating antigen specific immune responses (Hedley et al., columns 2-3 and 7-8). The fact that Hedley et al. teaches that transfection can take place *in vivo*, does not teach away from the clear suggestion to

transfect cells *in vitro/ex vivo* taught by Hedley et al. in column 12. Hedley et al. further provides motivation for introducing plasmid DNA encoding an antigen to dendritic cells and macrophages using biodegradable microspheres by teaching that DNA combined with biodegradable microparticles is efficiently phagocytosed by APCs and is an effective means for introducing nucleic acids into these cells (Hedley et al., column 8, lines 13-49). While Hedley exemplifies the transfection of macrophages, the teachings of Hedley et al. are not so limited. Hedley et al. clearly teaches the transfection of APCs, antigen presenting cells. Dendritic cells were well known at the time of filing as antigen presenting cells, as evidenced by Song et al. Further, Hedley et al. recognizes that dendritic cells are a legitimate target for the disclosed microparticle transfection when they state that the point of introduction of plasmid/microparticles to skin is the transfection of dendritic cells. Motivation for transfecting dendritic *ex vivo/in vitro* is derived primarily from the teachings of the primary reference, Song et al., who clearly teach and provide motivation for transfecting dendritic cells *ex vivo*, see above. However, Hedley et al. also teaches *ex vivo* transfection. In column 12, lines 23-30, Hedley et al. clearly states, "For in vitro/ex vivo use, the suspension of microparticles can be added either to cultured adherent mammalian cells or to a cell suspension". Thus, Hedley et al. clearly contemplates *ex vivo* transfection of APCs. This teaching is not limited to macrophages and includes other types of antigen presenting cells such as dendritic cells. Again, Song et al. already teaches the transfection of dendritic cells, Hedley is cited to provide motivation for using microparticles as a transfection agent. Thus, applicant's arguments that Hedley et al. only provide motivation for *in vivo* transfection of dendritic cells is not found persuasive.

The applicants further reiterate their argument that the successful transfection of macrophages exemplified by Hedley et al. does not provide a reasonable expectation of success for transfection of dendritic cells because dendritic cells and macrophages have different characteristics, "including the relative ease of transfection using non-viral means". However, as stated in the previous office actions, the prior art contains numerous successful examples of the transfection of dendritic cells *ex vivo/in vitro* using non-viral means such as plasmid DNA, either alone or in combination with liposomes or even gold beads (see Yang et al., Manickan et al., Spahn et al., and Tuting et al.). Thus, contrary to applicant's arguments, at the time of filing, the skilled artisan would have certainly had a reasonable expectation of success in transfecting dendritic cells using non-viral techniques.

In regards to Fattal et al., the applicant argues that Fattal et al. teaches antisense oligonucleotide rather than plasmid DNA and as such there would be no reasonable expectation of success in making and using CTAB microparticles according to Fattal et al. using plasmid DNA. The office disagrees, Figure 1 of Fattal et al. clearly demonstrates the chemical interaction between the oligonucleotide and the cationic microparticle. According to Fattal et al., it is the negatively charged phosphate groups of the nucleic acid chain that form ion pairs with the hydrophobic cations on the surface of the biodegradable microparticles (Fattal et al., page 139, column 1). Regardless of whether the nucleic acid is "antisense" oligonucleotide or nucleic acid present in a DNA plasmid, the nature of nucleic acids is that the backbone of the molecule is negatively charged. Thus, based on the nature of the negatively charged phosphate groups present in all nucleic acids, the skilled artisan would have had reasonable expectation that negatively charged plasmid DNA would likewise form ion pairs with CTAB or another cationic

detergent and would thus be capable of use in the microparticle/CTAB delivery vehicle taught by Fattal et al.. Applicants argument that the skilled artisan would not have been motivated to absorb plasmid DNA to microparticles to enhance plasmid DNA delivery to the nucleus is further not found persuasive because the claims do not recite methods of enhancing DNA delivery to the nucleus. The claims recites methods of transfecting dendritic cells comprising incubating dendritic cells with the transfection agent leading to the expression of an antigen. Any degree of expression would meet the limitations of the claims as written. Thus, the references are not required to provide a motivation for enhancing delivery of the plasmid to the cell nucleus. Fattal et al. was cited to provide motivation for including a cationic detergent in a composition comprising a microparticle and a polynucleotide. In fact, as noted in previous office actions, Fattal et al. provides clear motivation for including a cationic detergent in a microparticle by teaching that inclusion of a cationic detergent in microparticles increases the amount of polynucleotide associated with the polymer particles and increases the uptake of the nucleic acid by phagocytosis. Thus, the skilled artisan would have been amply motivated to include a cationic detergent in a microparticle composition comprising a polynucleotide in order to increase uptake of the polynucleotide by the target cell.

Regarding encapsulation versus adsorption, the previous office action stated that the claims as amended still encompass microparticles with encapsulated nucleic acid, see in particular claims 46 and 50 which specifically recite wherein a portion of the polynucleotide is entrapped within said microparticles. Thus, the claims as amended read on microparticles which have polynucleotide absorbed to the surface and encapsulated within the particle. Further, the interaction of the polynucleotide with the microparticle depends on the charge characteristics of

the microparticle itself and the presence or absence of additional molecules such as detergents or surfactants. The microparticles taught by Hedley et al. are not positively charged, thus combining the microparticles with the polynucleotide results primarily in encapsulation. On the other hand, Fattal et al. clearly teaches that adding a cationic detergent to the biodegradable microparticles results in particles with a positive charge such that the majority of the negatively charged polynucleotide absorbs onto the cationic surface rather than encapsulating within. Fattal et al. provides a useful diagram of the interactions on page 139, Figure 1. Combining the teachings of Song et al., Hedley et al., and Fattal et al. would thus result in microparticles with primarily adsorbed polynucleotide on the surface of the particle. Motivation for combining the teachings of Fattal et al. with those of Song et al. and Hedley et al., as discussed in detail above, rests in the teachings of Fattal et al. that inclusion of a cationic detergent in microparticles increases the amount of polynucleotide associated with the polymer particles and increases the uptake of the nucleic acid by phagocytosis.

Thus, for the reasons discussed above, applicant's arguments have not been found persuasive in overcoming the instant grounds of rejection of the claims as written.

Claim Objections

The objection to claims 52-53 under 37 CFR 1.75(c) has been withdrawn in view of applicant's amendments to the claims.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER